Clinical assessment of early brain function in infants with congenital heart disease

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Clinical assessment of early brain function in infants with congenital heart disease

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This commentary is on the original article by Hogan et al. on pages 1225–1231 of this issue.

Perinatal adverse events may disrupt neuronal structures and connections in the developing brain. In such cases, it has been hypothesized that functional outcome can be improved by stimulating and activating spared corticospinal tract axons, for example in infants with cerebral palsy.[1] Improved outcomes following stimulation through activation of spared neuronal structures after brain injury could also be considered for infants with congenital heart disease (CHD). It has become increasingly clear that infants with CHD are at risk of neurodevelopmental impairments.[2] It is therefore essential to identify these at-risk infants with CHD as early as possible when plasticity of the brain is the highest.

Hogan et al.[3] used the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) to assess neurobehavioral integrity in 67 infants with various types of CHD, before and after surgery. The NNNS is a standardized assessment tool to evaluate at-risk infants and is associated with neurodevelopmental outcome at 18 months in drug-exposed neonates and in neonates born preterm. Hogan et al. demonstrated that abnormal neurobehavioral patterns are common in infants with CHD; furthermore, they have distinctive neurobehavioral patterns in comparison with other at-risk populations, such as drug-exposed neonates.

Although the study by Hogan et al. is well performed and reports interesting findings, there are several limitations. First, they included a relatively small and very heterogeneous study population. Various types of CHD were included, almost one-third of the infants were born preterm and more than one-quarter were diagnosed with a genetic syndrome. The authors have analyzed differences between these subgroups, but the study population was too small to draw definite conclusions. Second, information on clinical characteristics (such as mechanical ventilation), use of medication (Prostaglandin E_1, sedatives), and Apgar scores at 5 minutes, was limited. All these characteristics could have influenced the NNNS scores and should therefore be accounted for.

It is still unknown which tool is best to predict neurodevelopmental outcome in infants with CHD. The NNNS is promising since it is non-invasive and could be applied immediately after birth. It would be interesting to investigate whether the NNNS predicts neurodevelopmental outcome in the infants studied by Hogan et al. Other tools that seem promising in predicting neurodevelopmental outcome of at-risk infants are magnetic resonance imaging (MRI), the General Movements Assessment (according to Prechtl's method), amplitude-integrated electroencephalography, and near-infrared spectroscopy.[1,4] A recent systematic review reported that in infants born preterm the NNNS was better for research purposes, while the General Movements Assessment was better for clinical utility and prediction of neurodevelopmental outcome.[5] Additional research is necessary to identify which tool is best to predict outcome in infants with CHD, especially since Hogan et al. found distinctive neurobehavioral patterns before and after surgery in these infants, in comparison with earlier studies on preterm-born neonates and drug-exposed neonates.

In conclusion, the study by Hogan et al. is of high clinical relevance as it demonstrates that it is possible to identify abnormal neurobehavioral patterns immediately after birth in infants with various types of CHD. Future studies are necessary to assess whether abnormal neurobehavioral patterns shortly after birth are associated with abnormal neurodevelopmental outcomes later in life. Furthermore, large multicenter studies should be conducted to allow for risk stratification according to the type of CHD, and to make a distinction between neonates born preterm and at term with CHD, and with isolated and syndromal CHD. Most importantly, we suggest a study of infants with CHD be performed combining several assessment tools such as (for example) the NNNS, the General Movements Assessment, MRI, near-infrared spectroscopy, and amplitude-integrated electroencephalography. This proposed study should be aimed at optimizing the identification of infants with CHD at risk of neurodevelopmental impairments, who may benefit most from early intervention.

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Clinical biomarkers for assessing neurodevelopmental outcome of infants born preterm

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It is well recognized that children with cerebral palsy (CP) often present with sensory deficits that limit proprioception, stereognosis, and tactile discrimination. Recent brain imaging studies have revealed that the neurophysiological nexus for these deficits likely resides in the aberrant somatosensory cortical processing of the peripheral stimulations arising from the hands and feet.[1,2] It seems logical that these somatosensory neuroimaging metrics might provide a non-invasive, early biomarker for identifying infants born preterm that are on course for adverse neurodevelopmental outcomes. Uncovering the predictive validity of the somatosensory neuroimaging measures would be valuable for informing parents about the potential long-term trajectory of their child's neurodevelopment, and for identifying infants that may benefit from alternative therapeutic approaches during critical developmental windows.

The retrospective study by Franckx et al.[3] aims to advance our understanding of a battery of clinical assessments (e.g. cranial ultrasound, magnetic resonance imaging [MRI], somatosensory evoked potentials) in identifying the long-term neurological outcome of infants born preterm at risk of developmental disabilities. Their analysis suggests that assessing the somatosensory cortical activity evoked after simulating the tibial nerve has limited utility for predicting an infant's future neurodevelopmental problems. Rather, cranial ultrasound during the first 2 weeks of life has a better ability to predict the likelihood that an infant would have CP or a cognitive developmental delay. Although these insights support the continued use of cranial ultrasound, the somatosensory results should be interpreted with caution because they are in opposition to a prior magnetoencephalography (MEG) study that suggests the uncharacteristic somatosensory evoked potentials predicts the potential for problematic neuromotor developmental outcomes in infants with a low birthweight.[4] Potentially, measures of the evoked somatosensory cortical activity used retrospectively may be of limited value because electroencephalography measures can be strongly distorted by the open fontanelle in the infant's skull, while the MEG neuromagnetic measurements are not.

Additional challenges reside in the ability to accurately assess neural activity based on a sensor positioned over the leg region of the somatosensory cortical topology (e.g. Cz). Unfortunately, sensor (scalp) time series are plagued with methodological limitations that affect accurate measures from the source of neural activity (i.e. volume conduction). Recent technological breakthroughs have resulted in the development of whole-head infant specific MEG devices that overcome these limitations. These ultramodern devices and associated advanced beamforming algorithms will likely provide conclusive evidence as to whether the evoked somatosensory cortical activity provides a reliable biomarker for assessing neurodevelopmental risk of infants born preterm.

Reliable metrics for predicting the likelihood of an uncharacteristic neurodevelopmental trajectory during infancy remains a pervasive Gordian knot in developmental medicine. Untangling this knot is challenging given that differential outcomes arise from numerous internal and external factors, including the developing brain's enormous capacity for neuroplasticity. The current best-practice guidelines recommend that a combination of clinical assessments (including MRI, Hammersmith Infant Neurological Examination, and General Movement Assessment) may lead to better prediction of an infant's neurodevelopmental trajectory at or before 5 months of age.[5] Furthermore, the overarching consensus is that single time-point measurements do not accurately capture an infant's neurological potential; but rather, repeated neurological and clinical assessments, coupled with clinical reasoning, are more likely to be prognostic.

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